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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,807	12/05/2000	Michael Wayne Graham	DAVI105.001A	1584

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,807	GRAHAM ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40 and 43-48* is/are pending in the application.

4a) Of the above claim(s) *14-16,19-26,29-33,39 and 44-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,17,18,27,28,34-38,40,43,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Non-Final Office Action is a reply to the "Response to Office Action" of 11 September 2003 (hereinafter, 11 September Paper) filed in response to the Non-Final Office Action mailed 7 March 2003 (hereinafter, 7 March Office Action). Claims 14-16,19-26, 29-33, 39 and 44-46 were withdrawn from consideration and claims 1-13, 17, 18, 27, 28, 34-38, 40, 43 and 47 were considered in the 7 March Office Action. Claims 1-10, 12, 17, 18, 27, 28, 34-37, 40, 43 and 47 were amended and claim 48 was added in the 11 September 2003 Paper. Claims 1-13, 17, 18, 27, 28, 34-38, 40, 43, 47 and 48 are presently under consideration.

Election/Restrictions

This application contains claims 14-16,19-26, 29-33, 39 and 44-46 drawn to an invention nonelected with traverse in the 7 March Office Action. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Amendment

Claim Rejections - 35 USC § 101

Rejection of claims 43 and 47 under 35 U.S.C. 101 as directed to non-statutory subject matter is withdrawn.

Claim Rejections - 35 USC § 112

Claims 1-13, 17, 18, 43 and 47 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter for reasons of record and herein below in the response to arguments.

Rejection of claims 27, 28, 36-38, 43 and 47 under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter is withdrawn in view of the amendments to the claims.

Claims 34, 35 and 40 stand rejected and newly added claim 48 is rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for reasons of record and herein below in the response to arguments.

Rejection of claims 11, 27, 28, 34-38, 40, 43 and 47 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn.

Double Patenting

Application No. 09/100,812 is now US Patent No. 6,573,099. Therefore, the provisional double patenting rejection set forth in the previous Office Action is withdrawn and a non-provisional double patenting rejection is made herein on the same grounds. Thus, claims 27 and 38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of the '099 patent (claim 2 of Application No. 09/100,812).

Claims 43 and 47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of the '099 patent (claim 38 of Application No. 09/100,812). Although the conflicting claims are not identical, they are not patentably distinct from each other for reasons set forth in the paragraph bridging pages 14-15 of the 7 March Office Action.

Claim Rejections - 35 USC § 102

Claims 27, 28, 36 and 37 stand rejected under 35 U.S.C. 102(b) as being anticipated by Dorer *et al.* (1994) 77:993-1002 for reasons of record and herein below in the response to arguments.

Claims 1, 2, 12, 17, 18, 27, 28, 38, 43 and 47 stand rejected under 35 U.S.C. 102(e) as being anticipated by Fire *et al.* (U.S. Patent No. 6,506,559) for reasons of record and herein below in the response to arguments.

Response to Arguments

Claim Rejections - 35 USC § 112

Claims 1-13, 17, 18, 43 and 47 are rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter because the specification, while being enabling for a method of repressing, delaying or otherwise reducing the expression of a target gene contained within the genome of an animal cell *in vitro* and an animal cell *in vitro* comprising a synthetic gene or genetic construct according to claims 27 or 38, respectively, does

not reasonably provide enablement for the method *in vivo* or a tissue, organ or whole organism comprising the synthetic gene or genetic construct according to claims 27 and 38, respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In response to the rejection of record, Applicant urges that the present claims are directed to methods of using RNAi which differs fundamentally form other methods of inhibiting RNA expression both in terms of observed effect and in terms of mechanism. While this distinction is acknowledged, the mere fact that RNAi is different from other methods cannot be taken as evidence of enablement for the method practiced *in vivo*, particularly in higher organisms such as mammals for which no experimental evidence of RNAi efficacy was available at the time of filing.

Applicant alleges that there was no factual support in the state of the art at the time of the invention to indicate that a person of ordinary skill in the art would not be able to make and use the presently claimed methods and criticizes the remarks of Fire cited in the previous Office Action as speculative at best and lacking factual support. In these remarks, Applicant appears to be relying on the undeveloped state of the art at the time of filing to support enablement. While it is true that there was very little published data on the use of RNAi *in vivo* at the time of filing, enablement for claims to an invention in an undeveloped art actually places a greater burden upon Applicant's specification to provide detailed description of how to make and use the invention. In fact, the undeveloped state of the art at the time of filling, which Applicant is

relying upon to rebut the statements of Fire, emphasizes the importance of working examples, of which there are none in the instant Specification, to evaluating enablement for the claims.

Applicant further alleges, "Fire's speculation has been directly controverted in the scientific literature for DNA expressed dsRNA *in vivo*" (page 15). Applicant cites Brummelkamp *et al.* (296 Science 550 (2002)) as demonstrating silencing in experiments mirroring those of the present application and urges that numerous studies in the art have demonstrated the effectiveness of the methods claimed in the present invention.

This argument is not found persuasive because a careful reading of Brummelkamp *et al.* and the supporting literature actually affirms Fire's prediction that "the simple protocols used for invertebrate and plant systems are unlikely to be effective" in mammals. In the first paragraph of the introduction (center column on page 550) Brummelkamp cites Elbashir *et al.* (2001) *Nature* 411:494-498, published 4 years after the effective filing date and 1 year after the actual filing date of the instant application, as teaching how to circumvent the strong non-specific cytotoxic response provoked by RNAi in most mammalian cells. Elbashir *et al.* teaches that attempts to detect potent and specific RNA interference in commonly used mammalian cell lines applying dsRNA that varies in size between 38 and 1,662 base pairs had failed (first paragraph of the introduction). Elbashir *et al.* goes on to teach that obtaining effective RNA interference in mammalian cells requires that the interfering RNAs be size limited to less than 30 nucleotides. It is also clear that Brummelkamp considers this size limitation, and not the DNA nature of the nucleic acids administered, to be among the critical elements for successful RNA interference in mammals. Nothing in the teachings of the instant specification would lead the skilled artisan to limit the size of the interfering nucleic acids to fewer than 30 nucleotides. Furthermore, in

discussing the requirements for effective expression of interfering RNAs *in situ*, Brummelkamp identifies the use of a polymerase-III H1 RNA gene promoter as another critical element "to provide a transcript lacking a poly adenosine tail", and "[m]ost important, the cleavage of the transcript at the termination site is after the second uridine…yielding a transcript resembling the ends of synthetic siRNAs, which also contain two 3' overhanging T or U nucleotides" (right column on page 550; see also Figure 1 and the caption thereto). Thus, Brummelkamp identifies structural elements such as the absence of a poly(A) tail and the presence of two 3' overhanging T or U residues as important considerations in designing effective interfering nucleic acid constructs. Neither of these limitations are considered in the instant application, and the inclusion of polyadenylation signals in many of the vector constructs, which would result in extended overhanging 3' poly(A) tracts, would seem to teach away from these structural limitations. Thus, the skilled artisan would not know how to make the constructs described by Brummelkamp based on the teachings available to the skilled artisan at the time of filing.

Next, Applicant discusses various teachings provided in the specification, which are mostly directed to recombinant DNA techniques that were routine in the art long before 2001 when Elbashir *et al.* announced, "for the first time, siRNA-mediated gene silencing in mammalian cells" (first full paragraph on page 497). None of the teachings found in the specification would enable the skilled artisan to practice the claimed invention *in vivo*.

Applicant criticizes the Examiner's use of the Deitz *et al.* patent in the previous enablement rejection because Applicant alleges that Dietz *et al.* is completely non-analogous art and fails to provide any factual basis to indicate that the present claims are not enabled. Applicant contends that lessons learned from the antisense art have no bearing on enablement for

claims directed to using RNAi. However, the teaching cited from Dietz *et al.* shows that suppressed of gene expression by 80%-90% of the normal level is not typically sufficient to reduce the biological effect of the gene product (7 March Office Action, page 8). This finding is clearly applicable to a discussion of enablement for any method which purports to provide useful suppression of gene expression regardless of the means or mechanism of suppression. Dietz *et al.* teaches that even a very high degree of suppression is not typically sufficient to provide a biological effect. Therefore, effective RNA interference will require, in many cases, a very high degree of suppression which could not, at the time of filing, be predictably obtained using the methods of the instant invention.

Applicant's arguments have been fully considered but are not found persuasive either individually or as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

Claims 34, 35, 40 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims were rejected because the only apparent utility for the claimed invention is xenotransplantation, which is not enabled by the specification.

In response, Applicant alleges that the rejection is based on the impermissible reading of limitations from the scientific literature into the claims. Applicant urges that the described α-1,3-galactosyl transferase in the specification is merely a non-limiting example of gene silencing not xenotransplantation. This argument is not deemed persuasive because the rejected claims are

actually limited to constructs specifically designed to target α-1,3-galactosyltransferase. Applicant is reminded each claim must be supported by a specific and substantial credible asserted utility or a well-established utility. As the specification does not assert any utility at all for constructs for suppressing α-1,3-galactosyl transferase, the Examiner is forced to consult the literature for a well-established utility. The Examiner can find no established utility for a reagent designed to suppress α-1,3-galactosyl transferase other than to prepare organs for xenotransplantation.

Furthermore, for the reasons set forth in the previous Office Action and herein above, the skilled artisan would not expect to be able to use the claimed invention to obtain useful suppression of α-1,3-galactosyl transferase using the teachings available in the art and specification at the time of filing. Although Applicant refers to a working example, the examiner can find no evidence of α-1,3-galactosyl transferase suppression by any means in the disclosure. Instead, Example 9 describes a series of tissue culture experiments but provides no results from these experiments.

Applicant's arguments have been fully considered but are not found persuasive individually or as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking an enabling disclosure.

Claim Rejections - 35 USC § 102

Claims 27, 28, 36 and 37 stand rejected under 35 U.S.C. 102(b) as being anticipated by Dorer *et al.* (1994) 77:993-1002 for reasons of record and herein below in the response to arguments.

In response to the rejection of record, Applicant argues that Dorer *et al.* does not anticipated the claims because Dorer *et al.* does not teach post-transcriptional repression of a target gene and provides no reference to delaying, repressing or otherwise reducing expression of a target gene by a separate genetic construct. These arguments have been fully considered but are not found persuasive. The art need not teach a particular mechanism of action to anticipate a claim. The rejected claims are directed to a synthetic gene comprising the structural limitations of at least two copies of a structural gene sequence which are substantially identical to the nucleotide sequence of a target gene or region thereof. The synthetic gene disclosed by Dorer *et al.* anticipates each of these structural limitations. With regard to the specified activity, if a prior art structure is capable of performing the intended use as recited in the claim, then it meets the claim. See, e.g., In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). Although Dorer *et al.* does not contemplate post-transcriptional repression, there is no evidence of record that the synthetic gene described therein is incapable of post-transcriptional repression; and, because Dorer *et al.* teaches all of the structural limitations of the claim, the claims are anticipated by Dorer *et al.*

Claims 1, 2, 12, 17, 18, 27, 28, 38, 43 and 47 stand rejected under 35 U.S.C. 102(e) as being anticipated by Fire *et al.* (U.S. Patent No. 6,506,559) for reasons of record and herein below in the response to arguments.

In response to the rejection of record, Applicant has amended the claims such that they are limited to introducing DNA to the animal cell, tissue or organ and argues that Fire *et al.* fails to teach these limitations. This argument is not deemed persuasive because, as pointed out in the

previous office action, Fire teaches that the double stranded RNA may be synthesized *in vivo* from a transgene or expression construct, which would require introducing DNA into a cell (see Fire *et al.*, paragraph bridging pages 8-9). Further, the discussion that immediately precedes this statement contemplates introducing the inhibitory nucleic acids into animal cells. Thus, it is clear that Fire *et al.* intends that the expression constructs be introduced into animal cells.

Next, Applicant alleges that the US Provisional application (60/068,562) to from which Fire *et al.* claims benefit does not support claims encompassing introducing DNA *in vivo* to the animal cell. On the contrary, in the first full paragraph on page 7 the '562 application teaches that the target cell may be an animal cell and the RNA may be synthesized *in vivo* by transcription from a transgene. Further, while discussing various means of delivering RNA into a target cell Fire *et al.* states, "[a] viral vector packaged into a viral particle would accomplish both efficient introduction of an expression vector into the cell and transcription of RNA encoded by the expression vector" (page 12, lines 10-12). Thus, the '562 application clearly supports introducing an expression vector into an animal cell according to the instant claim limitations.

Applicant's arguments have been fully considered but are not found persuasive individually or as a whole. Therefore, the claims stand rejected as anticipated by the Fire *et al.* patent.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Please note: Art Unit 1636 will be moving to the new USPTO facilities on 14 January 2004. After that date, Examiner Sullivan can be reached at 571-272-0779 and Examiner Yucel can be reached at 571-272-0781.

DMS

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER